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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/670,096	09/26/2000	Linda S. Mansfield	MSU 4.1-526	7494

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EXAMINER
BASKAR, PADMAVATHI

ART UNIT	PAPER NUMBER
1645	13

DATE MAILED: 09/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/670,096	MANSFIELD ET AL.	
	Examiner	Art Unit	
	Padmavathi v Baskar	1645	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

R sponse to Amendment

1. The response to the Office action filed on 6/16/03 has been entered into the record.

Claims 1-2 and 21 are pending in the application.

2. In view of amendment to the claims 1-2 and arguments of record, the rejection under 35 U.S.C. 102(b) as being anticipated by Liang et al is withdrawn.

Claim Rejections - 35 USC § 112, first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The rejection of claim 21 and newly amended claims 1 and 2 under 35 U.S.C. 112, first paragraph as containing subject mater which was not described in the specification in such a way so as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention is maintained as set forth in the previous office action.

Claims are directed to a composition and a method for treating an equid infected with *Sarcocystis neurona* comprising a mixture of isolated antibodies against 16 kD and isolated antibodies against 30kD antigens, wherein the antibodies are from serum of an animal immunized with the antigen, said antibodies are polyclonal and monoclonal antibodies.

The instant claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in re Wands, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the disclosed invention concerns a composition and a method for treating an equid infected with *S.neurona* comprising polyclonal and monoclonal antibodies. The state of the prior art indicates that the pathogenesis of Equine protozoal myeloencephalitis (EPM) is not fully known.

The state of the art also suggests that the prevalence of horses seropositive for *S.neurona* was approximately 45% in surveys conducted in different parts of USA and because

clinical EPM occurs in only a small proportion of seropositive horses, it is important and necessary to identify factors that govern progression from an apparent infection to clinically evident neurological disease (see page 198, first three paragraphs from Cutler et al 2001).

The specification discloses that the antibodies of the instant claims are intended for use as "pharmaceutical /therapeutics" useful for treating *S.neurona* infection in an equid. However, the specification does not teach any *in vivo* method using of the claimed antibodies for treating EPM disease in horses. The treatment of *S.neurona* infection in an equid with antibodies is highly complex and unpredictable. As taught by the prior art, Liang et al 1998 (Infection and Immunity; 66 (5) 1834-1838) it is apparent that not all antibodies generated to an antigen will neutralize the protein. Further, Liang *et al.* teach that '[A] although *S.neurona* was sensitive to specific antibodies, a 10-min exposure to antiserum was required to yield a significant reduction in parasite production. This may partially explain why protective antibodies to some apicomplexan parasites are effective *in vitro* but not *in vivo*. Newly released parasites are exposed to serum for a shorter time *in vivo*, and the access of neutralization-sensitive epitopes to antibody may be limited' (page 1837, right column, 3rd paragraph). Further, Liang *et al.* conclude while Sn 16 kD and Sn 14 kD antigens are expressed *in vivo,* further investigation of these candidate antigens is necessary for inclusion in a vaccine (page 1837, bridging paragraphs of first and second columns). The results of and conclusion by Liang *et al.* clearly indicates that *in vitro* data does not necessarily correlate to or be extendable to *in vivo*. Whether the claimed composition prevents the spread of *S.neurona* to the nervous system and CSF is not known and needs to be experimented. The specification does not provide evidence that the claimed isolated antibodies (passive immunization with antibodies) either prevent the equid from infection or prevent the spread of *S. neurona* to the nervous system and CSF. Furthermore, it is unclear whether such an immunotherapy can be used to treat an ongoing infection. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). In light of the teachings of Liang *et al* that the ability of an antibody to function *in vitro* does not correlate to function *in vivo,* the instant specification has not given the necessary teaching to provide a link between the proposed antibody and treatment of the infection. In addition, the specific antibodies, which bind to 16kD and 30 kD antigens required to practice the claimed invention, are not disclosed in the instant specification. The high degree of unpredictability associated with the claimed method underscores the need to provide teachings in the specification that would provide the artisan with specific treatment regimens that achieve a therapeutic benefit; however, the specification does not provide such guidance and fails to provide the necessary guidance. Further, as indicated by Liang *et al.*, one cannot predict the activity of an antigen for use in a vaccine from *in vitro* data. The specification only discloses multiple isolates of merozoites have been cultured from opossum derived *Sarcocystis* sporocyst (pages 37-44). However, the specification does not disclose 16 kD and 30kD antigens, comprising a mixture of isolated antibodies against 16 kD and isolated antibodies against 30kD antigens and a method of treating an equid using these antibodies. The specification, however, provides no working examples demonstrating (i.e., guidance) enablement for the claimed composition or a method. The specification only teaches culturing sporocyst and merozoites. Further the specification lacks support for a method of treating an equid with *S.neurona* infection. It is not clear whether or not all horses that are exposed to S.neurona infection are chosen to treat or those horses that show clinical signs of symptoms are treated since the naturally infected horses do develop antibodies to merozoites. Further, the specification fails to indicate that the claimed is able to control the systemic infection from spreading to central nervous system after merozoites pass through the vascular endothelium of the blood-brain barrier that causes EPM. The specification does not teach specific antibodies to 16kD and

30kD antigens that are able to treat infection. In view of the state of the art, the amount of guidance provided by the specification (i.e., lack of working examples in the specification) and the nature of invention, a method of specifically sufficient one skilled in the art to make and/or use the invention as claimed. Therefore a composition for treating infection and a method for treating an equid infected with *S.neurona* comprising a mixture of isolated antibodies against 16 kD and isolated antibodies against 30kD antigens must be considered highly unpredictable, requiring a specific demonstration of efficacy on a case-by-case basis. Absent such demonstration, the invention would require undue experimentation to practice as claimed.

Applicants arguments filed in Appeals Brief, Paper # 12 have been fully considered but they are not deemed to be persuasive.

Applicant agrees that Liang et al teach that antisera from horses with EPM contain antibodies against immunodominant merozoite antigens 11, 14, 16 and 30kD from *S.neurona.* and antibodies against 14 and 16kD are neutralizing *in vitro.* However, Applicant on the other hand states that if one skilled in the art relied upon the teachings of Liang for guidance, they would have mistakenly believed that the antibodies against 30kD are non-neutralizing and provides Declaration under 37C.F.R 1.132 (Appendix B) to show evidence that both antibodies to16 and 30kD neutralize merozoites in vitro.

The Declaration provided by the applicant is not sufficient to overcome the rejection for the following reasons: The Declaration does not provide any evidence that the claimed composition comprising said antibodies are used for treating an equid infected with S.neurona. Further, the Declaration does not show any evidence that antibodies would stop the spread of S.neurona infection to the nervous system (CNS) that causes EPM as applicant is claiming a method of treating an equid with infection that causes EPM. Therefore, it is necessary to show the data in support of the treatment of EPM disease with antibodies to 30kD and 16 kD. The Declaration provides evidence that the antibodies to 30kD and 16 kD neutralize the merozoites *in vitro* (neutralization assays) only.

Applicant further states that Liang et al teach antibodies to 30kD are not neutralizing. However, Liang et al clearly recognizes the problem for lack of neutralization with antibodies to 30kD and explains that the serum or CSF contains antibodies to 30kD antigens from other Sarcocystis species (see page1837, left column, first paragraph). Therefore, Liang et al do not indicate that antibodies to 30kD antigen of S.neurona are not neutralizing in vivo.

The examiner in Paper numbers 4, 6 and 8 made it clear on the record that the claims are not enabled for the following reasons:

a. The specification provides no guidance and no working examples for the claimed therapeutic composition and a method of treating an equid with infection.

b. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03) for in vivo studies.

c. The state of the art indicates that 10 minute exposure to antiserum was required to yield significant reduction in parasite production even in *in vitro* assays and this explains why protective antibodies to some apicomplexan parasites are effective in vitro but not in vivo (see page 1837, 3rd paragraph, left column) because newly released parasites in vivo are exposed to serum for a short time and the access to neutralizing epitopes is limited (see page 1837, 3rd paragraph, left column) in *in vivo* conditions.

The examiner has not rejected the claims solely based on *in vitro* neutralization assays as taught by Liang et al but raised the issue of unpredictability based on the lack of support in this undeveloped art as stated above and applicant has not provided any evidence on the efficacy of these antibodies in treating infected horses (see paper # 8, paragraph, 3, last three lines).

As applicant states that (page 12 Applicant's after final amendment filed on 4/28/03 and page 14 of appeals brief 6/16/03) the horses with EPM have an inadequate immune response

(antibodies), which is not sufficient to prevent entry of the parasite in to CNS and that boosting the immune response with antibodies against 16kD and 30kD antigens might provide sufficient boost to an infected horses immune response to inhibit entry of the parasite to CSF.

It is the position of the examiner that the art indicates the high rate of exposure to *S.neurona* and the relatively low incidence of clinical EPM and most horses develop an effective immunity that may prevent entry of the parasite into the central nervous system. However, it is possible in case of EPM that the parasite continues to undergo merogony (see Fenger et al 1997, page 923, upper right column) in CNS and changes its antigenicity and therefore the antibodies to the claimed antigens may not be able to eliminate merozoites in CNS. It is known in the art that the parasite changes its antigenicity at different stages of its life cycle. Therefore, the antigens expressed by merozoites before the EPM and after EPM may not be the same. The state of the art suggests that treatment with drugs like pyrimethamine –sulfonamide in combination with a competent immune response eventually eliminates merozoites (see Fenger et al 1997, page 926, right column, fourth paragraph). Therefore, it is important to provide evidence that the treatment with the claimed antibodies is sufficient to prevent entry of the parasite into CNS or complete elimination of merozoites from CNS.

Applicant cites Hines et al (Infection. Immunity 1995, 63; 349-352) to support that a second antigen was required to be effective in protecting the immunized cattle against a challenge. However, this art is not relevant since the claimed invention is not drawn to Babesia bovis and it is a different parasite that infects Cattle. Therefore, the rejection of record is maintained for the reasons set forth as above.

Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 2 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 21 are rejected as being vague and indefinite for the recitation of "monoclonal antibodies"

It is not clear how monoclonal antibodies are obtained from serum of an animal immunized with the antigen. The specification on page 27 recites that monoclonal antibodies can be made using hybridomas.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.

9/2/03

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9/11/03